Primary Prevention of Cardiovascular Events With Aspirin in Patients With Diabetes

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Although aspirin is one of our oldest pharmacological agents and much is known about it, our understanding of the particulars of its use as a preventive measure for cardiovascular disease (CVD) still resides in the domain of debate. Clearly, aspirin does offer some benefit in reducing the risk of CVD, but questions remain regarding the choice of patients and the optimal dose.

Patients with diabetes comprise a special population and are often prescribed aspirin for its potential cardiovascular risk-reductive action. This brief article reviews the use of aspirin in this population as a primary preventive measure. It focuses on several recently released position statements, including one recently co-issued by the American Diabetes Association (ADA), the American Heart Association (AHA), and the American College of Cardiology Foundation (ACCF).

Brief History

SALICIN, a natural precursor of aspirin found in willow bark and leaves, was used during the time of Hippocrates (400 BC) for the attenuation of pain and as an anti-pyretic. In the 1800s, aspirin was synthesized from the spirea plant (which is rich in salicin), and by 1899, the Bayer pharmaceutical company was distributing aspirin to physicians for use in their patients.

Aspirin was typically used for the management of pain, fever, and inflammation, but in 1948, Dr. Lawrence Craven, using only his intuition and empirical observations, noted that his patients treated with aspirin did not suffer heart attacks. Based on this notion, he routinely prescribed aspirin to his patients as a preventive measure. Ironically, in 1957, Craven died at the age of 74 of a myocardial infarction (MI), while denying himself aspirin therapy because he fell out of the age range that he felt benefited from treatment (45–65 years). It is interesting to note that his initial recommendations were fairly consistent with today’s data-based recommendations.

The elucidation of aspirin’s mechanisms of action continued to be worked out during the subsequent decades. Today, aspirin-induced inhibition of platelet aggregation is considered the most likely cause of aspirin’s cardioprotective effect.

Aspirin’s role as a cardioprotective medication was solidified with the publication of the Physician’s Health Study in 1989. This landmark trial confirmed Craven’s initial hypothesis that the use of low-dose aspirin could reduce the incidence of MIs. The study, a randomized, double-blind, placebo-controlled trial in > 22,000 physicians, demonstrated a 44% reduction in the risk of MI in subjects taking 325 mg of aspirin every other day. A plethora of studies have been conducted since then, and although questions regarding particular details, such as dose, are still being evaluated, it is widely accepted that low-dose aspirin can reduce the risk of both MI and stroke.

This pharmacotherapeutic modality has been, and remains, of great interest to providers managing patients with diabetes. Although the burden of CVD in our society as a whole is great, it is even greater for the diabetic population. Patients with diabetes are at a two- to four-fold greater risk of CVD than their nondiabetic counterparts.
individuals with diabetes who are > 65 years of age, 68% of deaths are the result of coronary heart disease, and about 16% are secondary to stroke. Therefore, measures that potentially afford primary risk reduction of CVD are of great significance to patients with diabetes.

Overview of Consensus Statement Recommendations
Several consensus statements have been published regarding the use of aspirin in the primary prevention of CVD. Although there are some differences among the various statements, their overall direction all point toward expected benefits from low-dose aspirin via reduced cardiovascular risk in many patients with diabetes.

U.S. Preventive Services Task Force recommendations
The U.S. Preventive Services Task Force, established by the U.S. Department of Health and Human Services, has recently published a “Guide to Clinical Preventive Services,” which includes recommendations for the use of aspirin for the primary prevention of CVD. The task force recommends the use of aspirin for primary prevention of CVD in men who are 45–79 years of age and women who are 55–79 years of age in whom the potential benefit (MI in men, stroke in women) of ~ 75 mg daily seems as effective as higher doses and may be associated with less risk of gastrointestinal bleeding.

ADA recommendations
The American Diabetes Association (ADA) also publishes recommended guidelines for the use of aspirin for the primary prevention of CVD as part of its annual “Standards of Medical Care in Diabetes” statement. These guidelines currently suggest aspirin therapy in patients with either type 1 or type 2 diabetes who have an increased risk of CVD (i.e., a 10-year risk of > 10%). They also state that this includes most men > 50 years of age and most women > 60 years of age who have at least one additional risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). This effectively includes most patients with diabetes in this age range. They also state that there is not sufficient evidence to support the use of aspirin for primary prevention in lower-risk individuals. This included men < 50 years of age and women < 60 years of age who lack other significant risk factors for CVD.

The ADA Standards of Care also include a short discussion regarding the notion of altered platelet function resulting in a resistance to the effects of aspirin in patients with diabetes. Some have suggested that this aberration might necessitate the use of higher-dose aspirin in this population. The guidelines conclude that, although there may indeed be a so-called “aspirin resistance” in the platelets of patients with diabetes, “these observations alone are insufficient to empirically recommend at this time that higher doses of aspirin be used in the diabetic patient.”

ADA/AHA/ACCF scientific statement
The above-mentioned organizations recently released a position statement regarding the use of aspirin for primary prevention of CVD. This group completed a robust evaluation of the available data regarding this topic and focused on answering the following questions:
1. What is the evidence regarding aspirin to prevent initial cardiovascular events in people with diabetes?
2. How can we reconcile the results of different primary prevention trials?
3. What are the risks of aspirin, and are these similar or different for people with diabetes compared to those without?
4. What do we know about the recommended dosage or dosage range?
5. How can we integrate potential benefits and risks of aspirin to determine which patients with diabetes should receive aspirin for the primary prevention of cardiovascular events?
6. What are the needs for future research?

A discussion of the nuances of this statement is beyond the scope of this brief review, and interested readers are referred to reference 5 and to the summary of recommendations listed in Table 1. The group concludes that “the effect of aspirin for primary prevention of CVD events in adults with diabetes is currently unclear,” but follows that statement

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Table 1. Should Low-Dose Aspirin (75–162 mg Daily) Be Prescribed to Patients With Diabetes for Primary Prevention of Cardiovascular Events?

<table>
<thead>
<tr>
<th>YES (It is “reasonable”):</th>
<th>NO: For males &lt; 50 years of age and females &lt; 60 years of age who have no additional major risk factors (10-year risk of &lt; 5%)</th>
</tr>
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<tbody>
<tr>
<td>For most males &gt; 50 years of age and females &gt; 60 years of age who have one additional risk factor (e.g., family history of premature CVD, hypertension, smoking, dyslipidemia, or albuminuria) and who are not at an increased risk of bleeding</td>
<td></td>
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<tr>
<td>For patients with intermediate risk of CVD such as males &lt; 50 years of age and females &lt; 60 years of age who have one or more risk factors or for males &gt; 50 years of age and females &gt; 60 years of age with no risk factors (10-year risk of 5–10%) and who are not at an increased risk of bleeding</td>
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Pharmacy and Therapeutics
with the following opinions and recommendations:

The use of low-dose aspirin for primary prevention of CVD is “reasonable” for adults with diabetes with no previous history of vascular disease who are at increased risk of CVD (i.e., 10-year risk of >10%) and who are not at increased risk of bleeding. They further define increased risk of CVD in a similar manner to the ADA guidelines discussed above as most men >50 years of age and most women >60 years of age who have at least one additional risk factor (family history of premature CVD, hypertension, smoking, dyslipidemia, or albuminuria). Increased risk of bleeding is defined as a history of gastrointestinal bleeding, peptic ulcer disease, or the concurrent use of medications that might cause bleeding such as nonsteroidal anti-inflammatory drugs or warfarin.

Aspirin is not recommended for primary prevention of CVD in patients with diabetes who have a low risk of CVD, such as younger patients with one or more risk factors or older patients with no risk factors (10-year risk of 5–10%).

Regarding dose, the group states that “the optimal dose of aspirin for the prevention of cardiovascular events is not clearly established from the outcomes literature.” They recommend a dose range of 75–162 mg daily.5

Conclusion
Although there is still some disagreement among opinion leaders regarding the particulars of the use of aspirin for primary prevention of CVD in patients with diabetes, everyone agrees that aspirin therapy is an effective risk-reduction measure in many. Based on patients’ individual characteristics, family history, and medications, providers can use the guidelines described here to make an informed judgment regarding the use of aspirin for primary prevention in their patients.

References

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